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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/789,465	02/27/2004	Mahendra S. Rao	2923-5456.1US	5295

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EXAMINER	
NGUYEN, QUANG	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 11/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/789,465	RAO ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-44* is/are pending in the application.

4a) Of the above claim(s) *5-11,22-25 and 28-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,12-21,26 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/27/04; 6/18/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-44 are pending in the present application.

Applicant's election without traverse of Group I (claims 1-4, 12-21 and 26-27) in the reply filed on 11/07/05 is acknowledged. Applicants further elected the following species: (a) glial progenitor cells as a species of somatic stem or progenitor cells; (b) RNA pol II locus as the species of the regions of homology (Applicant inadvertently misspelled the elected species on page 8); (c) lipofection as a species of the selected method; and (d) platelet derived growth factor as a species of the growth factor. In light of the prior art resulted from the search performed, and upon further consideration the species restriction is withdrawn.

Accordingly, claims 5-11, 22-25 and 28-44 are withdrawn from further consideration because they are directed to non-elected inventions.

Claims 1-4, 12-21 and 26-27 are examined on the merits herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 21 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

The specification is not enabled for this particular claimed embodiment for the reasons discussed below.

1. The breadth of the claim

The claim is directed to a method of obtaining homologous recombination in any somatic stem or progenitor cells comprising the step of introducing any IRES protein at any locus of nucleic acid of the somatic stem or progenitor cells prior to inserting the nucleic acid encoding any gene of interest into the somatic stem or progenitor cells.

2. The state and the unpredictability of the prior art

At the effective filing date of the present application (1/13/03), although a targeting vector construct containing an internal ribosomal entry site (IRES) element has been used for genetically modifying cells *in vitro* (WO 99/21415; page 9, line 19 continues to line 3 of page 10), virtually nothing was known on the use of any IRES protein to be introduced into any gene locus of any cell for any purpose.

3. The amount of direction or guidance provided

The instant specification fails to provide any guidance for a skilled artisan in the art on how to make any IRES protein (please note a protein is made up of amino acid

residues) and how such a protein is introduced into any gene locus of any somatic stem or progenitor cell population under which conditions, so that it plays any role in the method for obtaining homologous recombination in somatic stem or progenitor cells. Since the prior art at the effective filing date of the present application does not provide any guidance with regard to the make and/or use of any IRES protein, it is incumbent upon the present application to do so. With the lack of sufficient guidance provided by the present disclosure, it would have required undue experimentation for a skilled artisan to make and/or use the method as claimed.

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issues set forth above, the unpredictability of the physiological art, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and/or use the instant broadly claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-4, 12-13, 15-17 and 19-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Capecchi et al (US Patent 5,631,153; IDS) as evidenced by Sedivy, J.M. (Proc. Natl. Acad. Sci. USA 95:9078-9081, 1998; IDS).

Capecchi et al teach the use of positive-negative selector (PNS) vectors for modifying a target DNA sequence contained in the genome of a target cell capable of homologous recombination such as ES cells, hematopoietic, epithelial, liver, lung, bone marrow, endothelial, mesenchymal, neural and muscle stem cells to correct a genetic defect or for the supplementation of the gene product of a defective gene through an *ex vivo* gene therapy approach (see at least the abstract; col. 16, lines 10-65; and claim 21). In an exemplification, Capecchi et al teach specifically the introduction of an exogenous functional factor VIII gene to the β-actin locus of endothelial cells isolated from a hemophiliac patient by electroporation of a PNS vector into said cells and detecting cells expressing the functional factor VIII (see example 4, cols. 25-26; Fig. 7C). By selecting for genetically modified hematopoietic, epithelial liver, lung, bone marrow, endothelial, mesenchymal, neural and muscle stem cells expressing a supplemental gene product, such modified somatic stem cells would also express TERT and telomerase activity as evidenced by the teachings of Sedivy that germ cells and some key stem cells are known to express telomerase catalytic activity (page 9079, left column, top of last paragraph). Please also note that the culture medium in which the aforementioned genetically modified somatic stem or progenitor cells are and used for transplantation is considered to be a pharmaceutically acceptable carrier.

Accordingly, the teachings of Capecchi et al meet all the limitation of the instant claims as written. Therefore, the instant claims are anticipated by the reference.

Claims 1-3, 12, 15 and 16-17 are rejected under 35 U.S.C. 102(e) as being anticipated by Economides et al. (US 2003/0003581 A1) as evidenced by Sedivy, J.M. (Proc. Natl. Acad. Sci. USA 95:9078-9081, 1998; IDS).

Economides et al teach a method of targeting a promoter-less selection cassette containing a gene of interest into transcriptionally active loci, particularly into the ROSA26 locus in eukaryotic cells, stem cells and embryonic stem cells (see at least Summary of the invention, **particularly paragraphs 27-35 on page 3**). Please note that a selective marker gene can be considered as a gene of interest. By selecting for these genetically modified stem cells, such modified stem cells would also express TERT and telomerase activity as evidenced by the teachings of Sedivy that germ cells and some key stem cells are known to express telomerase catalytic activity (page 9079, left column, top of last paragraph).

Accordingly, the teachings of Economides et al meet all the limitation of the instant claims as written. Therefore, the instant claims are anticipated by the reference.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 13-14, 19 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Capecchi et al (US Patent 5,631,153; IDS) in view of Rao et al. (US Patent 6,235,527).

Capecchi et al teach the use of positive-negative selector (PNS) vectors for modifying a target DNA sequence contained in the genome of a target cell capable of homologous recombination such as ES cells, hematopoietic, epithelial, liver, lung, bone marrow, endothelial, mesenchymal, neural and muscle stem cells to correct a genetic defect or for the supplementation of the gene product of a defective gene through an *ex vivo* gene therapy approach (see at least the abstract; col. 16, lines 10-65; and claim 21). In an exemplification, Capecchi et al teach specifically the introduction of an exogenous functional factor VIII gene to the β-actin locus of endothelial cells isolated from a hemophiliac patient by electroporation of a PNS vector into said cells and

detecting cells expressing the functional factor VIII (see example 4, cols. 25-26; Fig. 7C).

Capecchi et al do not specifically teach the preparation of homologous recombined somatic stem or progenitor cells, wherein the somatic stem or progenitor cells are glial progenitor cells, even though they teach to genetically modify hematopoietic, epithelial, liver, lung, bone marrow, endothelial, mesenchymal, neural and muscle stem cells to correct a genetic defect or for the supplementation of the gene product of a defective gene through an *ex vivo* gene therapy approach.

However, at the effective filing date of the present application Rao et al already disclosed the preparation of a pure, homogenous population of mammalian central nervous system glial restricted precursor cells, and that these cells can be genetically modified by any means known in the art (e.g., lipofection, calcium phosphate transfection, electroporation, infection of viruses) for delivery of therapeutic or other compounds that include a gene encoding a growth factor such as a nerve growth factor, brain-derived neurotrophic factor, neurotrophin-3, glia-derived neurotrophic factor (see at least the abstract; col. 13, line 63 continues to line 45 of col. 14; and col. 19, lines 4-18).

Accordingly, it would have been obvious for an ordinary skilled artisan in the art to modify the method of Capecchi et al by also genetically modifying the isolated pure, homogenous population of mammalian central nervous system glial restricted precursor cells of Rao et al. by homologous recombination for delivery a therapeutic compound that includes a gene encoding a growth factor.

An ordinary skilled artisan would have been motivated to carry out the above modification because the genetically modified glial restricted precursor cells can be used to supply factors that promote neuronal survival and/or axonal regeneration (e.g., nerve growth factor, brain-derived neurotrophic factor, neurotrophin-3, glia-derived neurotrophic factor, and other factors known in the arts due to the ability of the glial cells and their precursors to integrate effectively within a host parenchyma as taught by Rao et al (col. 19, lines 4-18). Additionally, gene targeting through homologous recombination avoids many problems associated with a random integration of a heterologous gene into the genome of cells such as a wide variation in the level of expression of such heterologous gene in transformed cells, disruption of endogenous genes which are necessary for the maturation, differentiation and/or viablility of the genetically modified cells as already noted by Capecchi et al (col. 2, lines 10-43).

An ordinary skilled artisan would have a reasonable expectation of success to carry out the above modification in light of the teachings of Capecchi et al and Rao et al., coupled with a high level of skills of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 1 and 26-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Capecchi et al (US Patent 5,631,153; IDS) in view of Rao et al. (US Patent 6,235,527) as applied to claims 1, 13-14, 19 and 26 above, and further in view of Weiss et al. (US Patent 5,750,376; IDS).

The combined teachings of Capecchi et al and Rao et al have been discussed above. However, none of the reference teaches specifically the use of a gene encoding a platelet growth factor as a gene of interest, for example.

However, at the effective filing date of the present application Weiss et al already taught to genetically modify neural stem cells to produce or increase the production of a biologically active substance such as PDGF, FGF, NGF, BDNF, neurotrophins, EGF that is useful in the treatment of a CNS disorder (col. 21, line 55 continues to lines 29 of col. 22).

Accordingly, it would have been obvious for an ordinary skilled artisan in the art to modify the combined teachings of Capecchi et al and Rao et al by genetically modifying the isolated pure, homogenous population of mammalian central nervous system glial restricted precursor cells of Rao et al. though homologous recombination for delivery a therapeutic compound that includes a gene encoding a platelet derived growth factor in light of the teaching of Weiss et al.

An ordinary skilled artisan would have been motivated to carry out the above modification because Weiss et al already taught the gene encoding PDGF to be introduced into a neural stem cell is useful in the treatment of a CNS disorder.

An ordinary skilled artisan would have a reasonable expectation of success to carry out the above modification in light of the teachings of Capecchi et al, Rao et al., and Weiss et al, coupled with a high level of skills of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 1 and 15-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Capecchi et al (US Patent 5,631,153; IDS) in view of Steeg et al. (Proc. Natl. Acad. Sci. USA 87:4680-4684, 1990).

The teachings of Capecchi et al have been disclosed above. However, Capecchi et al do not teach specifically to introduce the gene of interest into the RNApol II locus, preferably the large subunit of RNA polymerase II encoding gene locus or RNA polr2a locus, through homologous recombination.

However, at the effective filing date of the present application Steeg et al already introduced successfully point mutations into the endogenous murine gene that encodes the largest subunit of RNA polymerase II with a vector construct containing regions of homology from the large subunit of RNA polymerase II locus (see at lest the abstract).

Accordingly, it would have been obvious for an ordinary skilled artisan in the art to modify the teachings of Capecchi et al by selecting the RNApol II locus, including the large subunit of RNA polymerase II encoding gene locus or RNA polr2a locus to introduce a gene of interest though homologous recombination in light of the teachings of Steeg et al.

An ordinary skilled artisan would have been motivated to carry out the above modification because Steel et al. has successfully demonstrated that specific point

mutations can be introduced into the largest subunit of RNA polymerase II locus by gene targeting or homologous recombination.

An ordinary skilled artisan would have a reasonable expectation of success to carry out the above modification in light of the teachings of Capecchi et al, Steeg et al., coupled with a high level of skills of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1-4, 12-21 and 26-27 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-4, 12-21 and 26-27 of copending Application No. 10/867,628. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed.

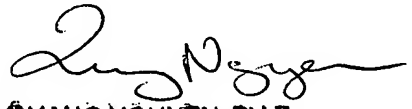
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's primary, Celine Qian, Ph.D., may be reached at (571) 272-0777, or SPE, Dave Nguyen, at (571) 272-0731.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.



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PATENT EXAMINER